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Non-invasive estimation of blood pressure using ultrasound contrast agents

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Abstract

Local blood pressure measurements provide important information on the state of health of organs in the body and can be used to diagnose diseases in the heart, lungs, and kidneys. This paper presents an experimental setup for investigating the ambient pressure sensitivity of a contrast agent using diagnostic ultrasound. The setup resembles a realistic clinical setup utilizing a single array transducer for transmit and receive. The ambient pressure sensitivity of SonoVue (Bracco, Milano, Italy) was measured twice using two different acoustic driving pressures, which were selected based on a preliminary experiment. To compensate for variations in bubble response and to make the estimates more robust, the relation between the energy of the subharmonic and the fundamental component was chosen as a measure over the subharmonic peak amplitude. The preliminary study revealed the growth stage of the subharmonic component to occur at acoustic driving pressures between 300 and 500 kPa. Based on this, the pressure sensitivity was investigated using a driving pressure of 485 and 500 kPa. At 485 kPa, a linear pressure sensitivity of 0.42 dB/kPa was found having a linear correlation coefficient of 0.94. The second measurement series at 485 kPa showed a sensitivity of 0.41 dB/kPa with a correlation coefficient of 0.89. Based on the measurements at 500 kPa, this acoustic driving pressure was concluded to be too high causing the bubbles to be destroyed. The pressure sensitivity for these two measurement series were 0.42 and 0.25 dB/kPa with linear correlation coefficients of 0.98 and 0.93, respectively.

Keywords: Blood pressure; contrast agent; pressure estimation

1. Introduction

Knowledge of the blood pressure locally in the body can help doctors to diagnose diseases in vessels and other organs that are related to the blood pressure. Today, two different approaches are already used in the hospital. One procedure is to use an A-cannula which is also used to measure the gases in the blood at the same time. This is most often used in intensive care units. Another procedure is to insert a catheter with a pressure sensor and guide it to the area of interest through the vessels. Both approaches are invasive and especially the presence of a thin plastic tube inside the body must be considered inconvenient to the patient and also connected to a certain risk. Besides, as the sensors are located inside the vessel of interest, both approaches introduce changes to the blood flow and thereby the

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blood pressure. Furthermore, it is not possible to monitor all areas inside the body using neither of these approaches. A noninvasive approach, which already exists, gives an estimate of the pressure gradient based on flow estimation and a modification of the Bernoulli equation 0. It was, however, concluded not to provide reliable or reproducible results by Strauss et al. 0 and Reddy et al. 0.

Due to the high compressibility of gas, microbubbles containing air or gas can be used as local pressure sensors 0, 0, 0. Fairbank and Scully 0 was the first to suggest the idea of using an ultrasound contrast agent (UCA) to measure the cardiac pressure noninvasively in 1977. They claimed that the acoustic properties of the microbubbles change when the size of the bubbles change. To measure these changes, they suggested measuring the shift in resonance frequency. However, they found the results to be inconclusive. Other suggestions to measure the resonance shift at that time were made by Tickner 0 in 1982, Ishihara et al. 0 in 1988, and Schlief and Poland 0 in 1993. Another approach was presented by Newhouse and Shankar 0, 0 in 1986. They showed theoretically and experimentally that accurate bubble size measurements are possible using a double frequency technique for determination of the sum and difference frequencies. The rapid dissolution time of free air bubbles, however, prevented any practical implementation at that time.

Since the introduction of the more stable second generation UCAs, new attempts to take advantage of the ambient pressure dependent acoustic properties have been initiated. In 1999, Bouakaz et al. 0, 0 presented an approach for measuring the disappearance time of free bubbles, which were generated at the region of interest by rupturing the contrast agent microbubbles using a low-frequency high acoustic amplitude pulse. Despite successful in vitro experiments and suggestions for further sensitivity improvements, no in vivo results or further investigations using this approach have been presented yet. Around the same time, Shi et al. 0 observed from experiments, using two single element transducers, that the subharmonic component of Levovist is highly sensitive to ambient pressure changes compared to the fundamental and the second harmonic component. They reported a 9.9 dB linear decrease of the peak amplitude of the subharmonic component when increasing the ambient pressure from 0 to 24.8 kPa (1 kPa = 7.5 mmHg). Recently, the same group has presented similar results for Sonazoid, which was found to have an average decrease of 13.3 dB 0. Furthermore, in 2005 they presented in vivo results for proof of concept of the capabilities of the subharmonic response 0. However, as the measurements were performed directly on the abdominal cavity and the aorta by incision of two dogs, this can hardly be characterized as noninvasive. Also in 2005, Adam et al. 0 did a thorough and interesting study to understand the mechanisms of acoustic scattering and attenuation of Optison (at the time Mallinckrodt Medical GmbH, Hennef, Germany) when subjected to ambient over pressure. One of the conclusions confirmed that the subharmonic of the transmitted frequency can be used to detect ambient pressure variations. Andersen and Jensen 0 have recently performed a parameter study to optimize the subharmonic sensitivity to ambient over pressure and found two very clear tendencies. First, the linear reduction of the subharmonic component, or the pressure sensitivity, is dependent on the acoustic driving pressure and peaks when in the upper end of the growth stage, which occurs when the acoustic driving pressure causes the subharmonic to increase rapidly from background noise level to clearly visible in the spectrum. Second, the investigation also showed a clear relation between ambient pressure sensitivity and the length of the driving pulse.

This paper presents an approach to experimentally investigate the fundamental and subharmonic response of a contrast agent as a function of the ambient pressure, which continuously is changed. Basically, the experimental setup consists of an airtight chamber and a single phased array transducer. Compared to a setup utilizing two transducers, which is not optimal in the clinic 0, this resembles a clinical setup more realistically. The setup was first used to investigate the current batch of SonoVue (Bracco, Milano, Italy) in respect to the acoustic pressure of the emitted ultrasound pulse. Next, the pressure sensitivity was measured using a standard ultrasound acquisition procedure and signal processing steps, which can easily be implemented in any commercial ultrasound scanner. Some part of this work has been presented at the 2008 IEEE International Ultrasonics Symposium 0.

2. Method

2.1. Experimental setup

Fig.1 shows a block diagram of the experimental setup used in the measurements. The measurement is controlled from a single standard PC equipped with connections for ethernet and serial communication running Matlab (The MathWorks Inc., Natick, MA) under Linux. The ultrasound acquisition is carried out using the experimental ultrasound scanner RASMUS 0, which is controlled from the PC through an ethernet connection. It is a real-time ultrasound system and provides full control of the transducer in both transmit and in receive. It is capable of storing 16 GBytes of raw ultrasound data with a sampling frequency of 40 MHz and a precision of 12 bits for offline processing, which is essential in an experiment like this. For the acquisition, a single 64 element phased array transducer (B-K Medical, Herlev, Denmark) is connected to the RASMUS system. It has a center frequency of 3 MHz and a –6 dB bandwidth of 60 percent. The transducer is sealed to the measuring chamber giving no barrier between the contrast agent and the transducer. The measuring chamber is airtight and consists of two parts separated by a rubber membrane. The bottom part has a volume of 605 ccm and can be filled with either water or saline. The walls are coated with acoustic damping material to reduce ultrasound reflections from prior emissions. It also has inlets for the transducer, fast injection of contrast agent, and a sensor to monitor the pressure within the chamber. To keep the bubbles in motion, a magnetic stirrer IKA RCT (IKA-Werke GmbH & Co. KG, Staufen, Germany) is used. The purpose of the lid, which has a dead volume of 75.9 ccm, is to change the pressure inside the chamber without mixing the inflated air with the bubbles injected into the liquid. The pressure is managed by a custom designed dual valve pressure controller PCD4-10PSIG (Alicat Scientific, Tucson, AZ). It has an external pressure sensor and is fully programmable in real time through a RS-232 serial interface connected to a PC. The compressed air is generated by a silent oil-less compressor OF301-4M (Jun-Air International A/S, Nørresundby, Denmark) providing a feed pressure of 4 bar. This is reduced to a constant feed pressure of 2 bar using a separate precision regulator from ATD Tools (Wentzville, MO).

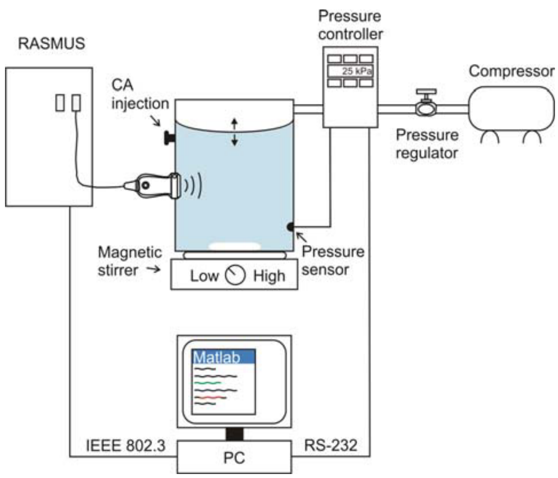

Fig.1 Block diagram of the measurement setup. The left part shows the ultrasound acquisition part. The right part illustrates the pressure management system.

2.2. Experimental procedure

2.2.1. Acoustic driving pressure

Two types of measurements were carried out. The response of SonoVue (Bracco, Milano, Italy) was initially investigated as a function of 14 different acoustic driving pressures denoted P_{ac}. At each acoustic pressure setting, N_{emis} = 50 cosine tapered pulses consisting of N_c = 32 cycles with a center frequency of f_0 = 4 MHz were emitted using a pulse repetition frequency of f_{prf} = 50 Hz. After the data acquisition, the energy of the subharmonic and the fundamental component was calculated using a bandwidth of 0.5 MHz centered around f_{sub} = 2 and f_0 = 4 MHz, respectively. For this experiment, 0.5 ml of Sonovue was injected into 0.6 l of saline. The setup parameters for the measurement are listed in Table 1.

Table 1. Setup parameters for the experiment investigating the dependence on the acoustic driving pressure.

Parameter	Designation	Unit
f_0	4.0	[MHz]
N_c	32	[cycles]
Shape	10 % cosine tapered	
P_{ac}	100 200 300 325 350	[kPa]
	375 400 450 485 500	
	550 600 700 900	
N_{emis}	50	[emissions]
f_{prf}	50	[Hz]
Contrast agent	SonoVue, batch 8A008D	

Table 2. Setup parameters for the experiment investigating the ambient pressure sensitivity. Only parameters which deviate from Table 1 are listed.

Parameter	Designation	Unit
P_{ac}	485 500	[kPa]
P_{ov}	0 5 10 15 20 25	[kPa]

2.2.2. Ambient pressure sensitivity

To investigate the ambient pressure sensitivity, the acoustic bubble response was measured at six different ambient pressures between 0 and 25 kPa. This corresponds to the common physiological blood pressure range in the human body. The measurement was initiated within 3 minutes after injection of 0.5 ml of SonoVue into 0.6 l of saline. At each ambient pressure, 50 lines were acquired using a pulse repetition frequency of 50 Hz. Every 2 seconds, the ambient pressure was increased in steps of 5 kPa until the peak ambient pressure of 25 kPa was reached. It was then decreased in steps of 5 kPa. The ambient pressure was allowed 1 second to adjust in between acquisition at each pressure setting. The entire measurement, thereby, lasted 21 seconds and provided two series of scattered ultrasound data at each ambient pressure, except at 25 kPa – one set when increasing the ambient pressure and another set when decreasing the ambient pressure. The emitted ultrasound pulse was a steered beam identical to the one used to investigate the acoustic driving pressure dependent behavior. Two similar experiments were carried out using an acoustic driving pressure of 485 and 500 kPa, respectively. These acoustic pressure settings were selected based on the initial experiment, which indicated this to be in the upper end of the subharmonic growth stage. The acquired data was first filtered, allowing only the subharmonic and the fundamental components to pass. Next, each acquisition line was beamformed and 25 data segments of 80 samples each were extracted, using a 50 percent overlap according to Welch 0, to estimate the power density spectrum. The periodogram was found using Bartlett's method 0 and applying a Hanning window to each segment before calculating the Fourier spectrum. Next, the energy of the subharmonic and fundamental component was calculated using a bandwidth of 0.5 MHz centered around the respective peak amplitude. To reduce factors like UCA concentration and time dependency, the relation between the energy of the subharmonic and the fundamental components is found before averaging over 10 consecutive emissions. As 50 lines are acquired, this yields 5 estimates at each ambient pressure set point. The measurement parameters that deviate from the first experiment listed in Table 1 are presented in Table 2.

3. Results

3.1. Acoustic driving pressure

Fig.2 shows the energy of the fundamental and subharmonic component calculated for each of the 14 different acoustic driving pressures. Looking at the fundamental component, an almost linear increase in energy is observed as the acoustic driving pressure is increased. The energy of the subharmonic component behaves, however, differently. For acoustic pressures below 300 kPa, almost no change in the amount of energy is seen and the subharmonic component is not (or almost not) visible in the spectra. For acoustic pressures between 300 and 500 kPa a rapid increase in energy is suddenly observed. This part is often referred to as the growth stage and implies that the subharmonic component gets more and more pronounced in the spectra. For acoustic pressure levels above 500 kPa, the increase in energy decays and this part is known as the saturation stage. In this stage, a general increase in energy for all frequencies has also been reported, indicating that the bubbles are being disrupted 0, 0.

3.2. Ambient pressure sensitivity

Based on the results in Section C.1, two different acoustic driving pressures have been selected to investigate the ambient pressure sensitivity. Before showing these results, an example of the ambient pressure management is first given. Next, the pressure sensitivity using an acoustic driving pressure of 485 kPa is presented in Section C.2.2 followed by the results using an acoustic pressure of 500 kPa in section C.2.2.

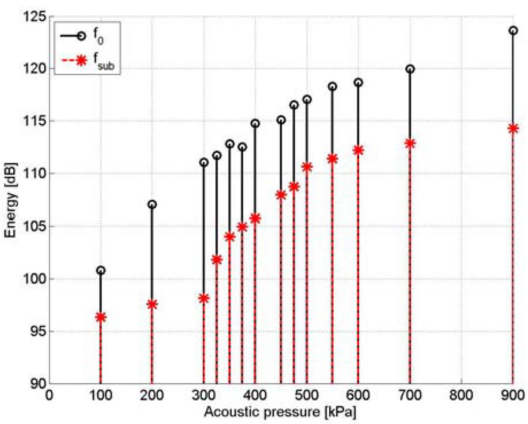

Fig.2 Energy of the fundamental and subharmonic component as function of the acoustic driving pressure.

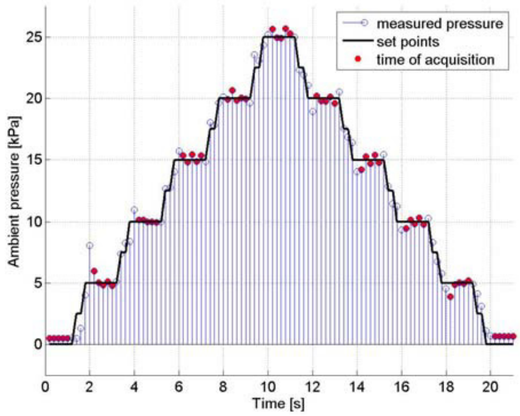

Fig.3 Example of the ambient pressure measured inside the chamber during an experiment. This is for the measurement with P_{ac} = 500 kPa. The solid thick line indicates the pressure set points transmitted to the pressure controller. Finally, the dots inside the circles denote the time of ultrasound data acquisition.

3.2.1. Ambient pressure management

As the pressure logs, which summarizes the ambient pressure control during the measurement, are very similar, only the one for P_{ac} = 500 kPa is presented here. Fig.3 shows the instantaneous pressure, measured by the sensor inside the chamber and the desired pressure transmitted from the PC. The time intervals for acquiring the ultrasound data is furthermore indicated by the filled circles. As can be seen in Fig.3, the pressure measured inside the chamber is following the desired set points closely, except for a single high overshoot when increasing the ambient pressure to 5 kPa at the very beginning. When focusing on the ambient pressure measured at the time of ultrasound acquisition, only two time intervals has a deviation of 1 kPa or more. This is observed once at each of the two pressure settings at 5 kPa. Excluding these, the maximum deviation from the desired ambient pressure is 0.7 kPa. This occurs at the second setting at 15 kPa and yields at the same time the maximum relative deviation which is 5.3 %.

3.2.2. Acoustic driving pressure of 485 kPa

Fig.4 shows the calculated energy of the fundamental and the subharmonic component as a function of ambient pressure and in order of time for the respective measurements. The energy of the fundamental component is more or less stable until about P_{ov} = 25 kPa, where it seems to start decreasing. The subharmonic component seems to drop from the beginning of the experiment to the end. According to Shi and colleagues 0, 0, this was expected for the first six measurement points. But the fact that the energy continues to drop for at least the next two measurement points, P_{ov} = [20 15] kPa, could indicate that the bubbles are being dissolved.

When looking at the results for pressure setting one (0 Pa) and six (25 kPa), constituting the first measurement series, the energy of the fundamental component changes by 0.6 dB. In the same interval, the energy of the subharmonic component is reduced by 9.2 dB. Both these observations correspond well to the results presented in 0 and 0. However, the fluctuating nature and the overall decrease in energy seen in Fig.4 necessitate a more robust measure. Therefore, the relation between the energy of the subharmonic and the fundamental component is used in this experiment. The result is shown in top of Fig.5, which also includes the standard deviation of the five estimates at each ambient pressure setting.

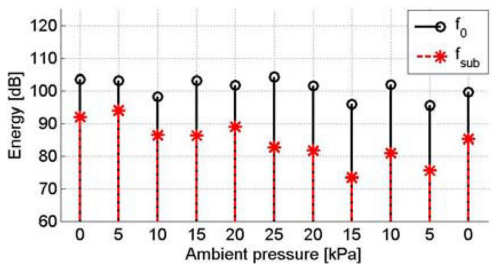

Fig.4 Energy of the fundamental and subharmonic component estimated at the 11 different ambient pressures when using an acoustic pressure of 485 kPa. Each value is the mean of five estimates, which has been found based on 200 separate spectra each.

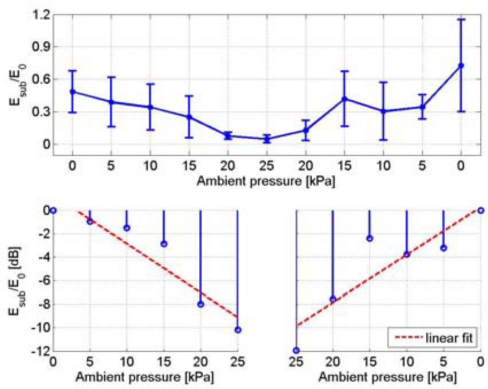

Fig.5 The top plot shows the relation between the energy of the subharmonic and the fundamental component estimated at each of the 11 ambient pressures. The error bars show the standard deviation, which has been calculated based on five estimates. Below, the relation has been normalized and the logarithm applied for each of the two measurement series.

According to Welch's method, the standard deviation scales with the number of segments used in the periodogram 0. As 20 segments in each of 10 emissions are used for the estimate, the minimum standard deviation expected is $\sigma^2 \approx P_x^2/200$, where P_x is the power spectrum. Looking at the standard deviation in Fig.5, it is rather high compared to this. Part of the reason can be because of the low pulse repetition frequency, which was selected not to harm the bubbles too much and to prevent acquisition of reverberations. However, to understand the deviation fully and to improve the accuracy, a more thorough investigation regarding the choice on number of segments and emissions, as well as the f_{prf}, should be carried out. Despite the high standard deviation, a clear trend can still be observed from the two measurement series in the plot in top of Fig.5. As the ambient pressure is increased, the relationship seems to drop. To investigate this further, each measurement series has been normalized according to its peak value at 0 Pa before applying the logarithm. The results are shown in the two bottom plots in Fig.5. The dashed lines indicate a first order polynomial fit, which minimizes the error in a least-squares sense. For the first measurement series displayed to the bottom left in Fig.5, the linear fit indicates an ambient pressure sensitivity of 0.42 dB/kPa with a linear correlation coefficient of 0.94. In the second measurement series, the pressure sensitivity is 0.41 dB/kPa having a correlation coefficient of 0.89.

3.2.3. Acoustic driving pressure of 500 kPa

The energy of the fundamental and the subharmonic component is shown in Fig.6 as a function of the ambient pressure when using an acoustic driving pressure of 500 kPa. Comparing this to Fig.4, a somewhat different behavior is observed. First of all, the energy of the fundamental component is seen to drop significantly as the ambient pressure is increased or over time, or a combination of this. This continues until the ambient pressure is decreased to above 20 kPa, where a linear increase is suddenly observed. However, comparing the energy of the fundamental component at pressure setting one (0 Pa) and 11 (0 Pa), is has decreased by 10.4 dB. This indicates that a lot of bubbles have been destroyed most likely due to the high acoustic pressure, but possible also because of the ambient pressure effects. The subharmonic component behaves almost the same as the fundamental, except it does not increase further as the ambient pressure is decreased from 10 to 0 kPa in the second measurement series. One explanation for this could be that the size of the bubbles left at this point has reduced and in that way makes it more difficult to generate a subharmonic component at 2 MHz.

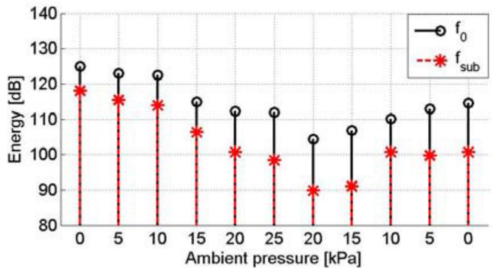

Fig.6 Energy of the fundamental and subharmonic component estimated at 11 different ambient pressures when using an acoustic driving pressure of 500 kPa.

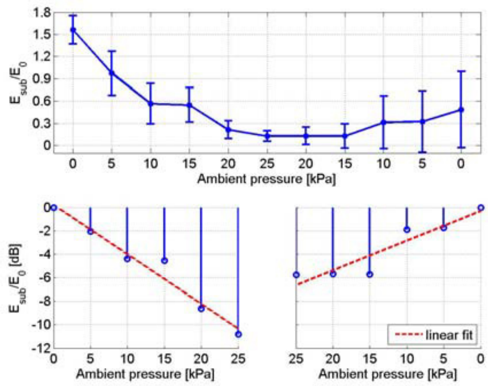

Fig.7 The plot on top shows the relation between the energy of the subharmonic and the fundamental component when using an acoustic driving pressure of 500 kPa. Below, the corresponding reduction plots for each measurement set are shown.

Despite the clear indication of bubble destruction observed in Fig.6, the relation between the energy of the subharmonic and the fundamental component has still been investigated and is shown in top of Fig.7. Looking at the first measurement series when decreasing the ambient pressure, an almost completely linear reduction is seen. In fact, the correlation coefficient calculated for the first order polynomial fit is 0.98. The linear fit also indicates an ambient pressure sensitivity of 0.42 dB/kPa, which is the same as for P_{ac} = 485 kPa. This is not as expected according to the simulation study by Andersen and Jensen 0, which predicted an increase in sensitivity as the acoustic driving pressure is increased. This deviation, thereby, confirms the suggestion that the acoustic driving pressure was selected too high, which then destroys the bubbles. This theory is corroborated further when drawing the attention to the second measurement series in the lower right corner of Fig.7. In this case, the linear fit reveals that the ambient pressure sensitivity has been reduced to 0.25 dB/kPa ($R = 0.93$). To investigate the conclusions in 0 it is, therefore, suggested to use a lower acoustic driving pressure in future experiments.

4. Conclusion

A realistic clinical setup has been used to examine the pressure sensitivity of an ultrasound contrast agent. The setup consists of an airtight chamber with connections for a single array transducer and inlets for automatic regulation of the ambient pressure and fast injection of contrast agent. The acquisition of raw ultrasound data and management of the ambient pressure is controlled from a single standard PC. The setup was first used to measure the acoustic response of SonoVue as a function of acoustic driving pressure. The growth period of the subharmonic component was found to be in the interval between 300 and 500 kPa. A driving pressure of 485 and 500 kPa, respectively, where next used to investigate the ambient pressure sensitivity. The driving pressure at 500 kPa where found to cause too much bubble destruction to be useful in a practical situation. At 485 kPa, the ambient pressure sensitivity was found to be 0.42 and 0.41 for two consecutive measurement series. The linear correlation coefficients for these measurements were 0.94 and 0.89, respectively.

Aknowledgements

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